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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kenji Fukudome and Charles T. Esmon

Serial No.: 09/378,261 Art Unit: 1647

Filed: August 20, 1999 Examiner: Stephen Gucker

#20
M.G.
12/5/02

For: *CLONING AND REGULATION OF AN ENDOTHELIAL CELL PROTEIN C/ ACTIVATED C PROTEIN C RECEPTOR*

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 16, 17 and 27-30 in the Office Action mailed March 26, 2002, in the above-identified patent application. A Notice of Appeal was mailed on August 22, 2002. Enclosed is a check in the amount of $215.00 for the filing of this Appeal Brief for a small entity with a one month extension of time along with a petition for a one month extension of time, up to an including November 22, 2002. It is believed that no additional fee is required with this submission. If an additional fee is required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real parties in interest of this application are the assignee, Oklahoma Medical Research Foundation, and the licensee, Diagnostica Stago.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 16, 17 and 24-30 are pending. Claims 16, 17 and 27-30 are on appeal. Claims 24-26 were objected to. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended by the amendment mailed November 19, 2002. An amendment after final rejection was mailed on June 26, 2002. In the Advisory Action mailed July 15, 2002, the Examiner indicated that this amendment would not be entered. An amendment accompanies this appeal brief which amends claim 24 into independent form, and corrects the dependency of claim 26 to claim 24. The amendment also deletes the reference to nucleic acids in claim 16 and cancels claim 27. The appendix sets forth the claims on appeal based on the claims as pending prior to entry of this amendment.

(5) SUMMARY OF THE INVENTION

The claims are directed to a method for enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor (claim 16 as originally filed). This method entails administering to a patient an amount of a compound blocking binding of protein C or activated protein C to the receptor by

binding to the endothelial cell protein C/activated protein C receptor (claim 16 as originally filed, and page 21, lines 8-12). The compound to be administered can be either antibodies and fragments of antibodies to the receptor, nucleic acid sequences inhibiting expression of the receptor, synthetic or natural compounds other than proteins, peptides or nucleic acid sequences that inhibit binding (claim 17 as originally filed). If the compound is an antibody or antibody fragment immunoreactive with the receptor, it can be a humanized antibody (page 21, line 19; pages 21-22). The compound can be an oligonucleotide or a receptor fragment (pages 29-31; page 32). The compound can also be combined in a pharmaceutically acceptable carrier (page 23, lines 14-23), and administered in an amount effective to enhance an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor (claim 16 as originally filed).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 16, 17 and 27-30 are enabled as required by 35 U.S.C. § 112, first paragraph, and

(2) whether claims 16, 17 and 27-30 comply with the written description requirement as required by 35 U.S.C. § 112, first paragraph

(7) GROUPING OF CLAIMS

The claims do not stand or fall together as described below.

(8) ARGUMENTS

a) The Claimed Invention

The claims are directed to a method for enhancing the protein C-mediated inflammatory response by inhibiting the binding of protein C/ activated protein C to the endothelial protein C receptor (EPCR). Protein C is a naturally occurring vitamin K-dependent plasma anticoagulant, whose anticoagulant effect is largely due to rapid inactivation of factors Va and VIIIa. The Protein C molecule, which occurs naturally and is found in the bloodstream, has no biological effect by itself, but during coagulation, the molecule goes through four complex chemical modifications to form endogenous (or naturally occurring) Activated Protein C (APC), a biologically active molecule that has multiple properties, including anti-thrombolytic, anti-inflammatory, and pro-fibrinolytic effects. Protein C inhibits inflammation by reducing the production of IL-1, IL-6, and TNF-beta by monocytes.

EPCR is a type I transmembrane receptor that is highly expressed on the endothelium of large blood vessels, and is equally specific for protein C and activated protein C. Binding of protein C to EPCR inhibits an inflammatory response (page16, line 9). The Appellants have cloned and characterized the receptor for protein C and described methods to generate antibodies/ antibody fragments to EPCR, and methods to design and screen molecules using computer-assisted drug design (sections beginning on pages 23 and 26).

In some situations, it is desirable to enhance the inflammatory response, for example in treating solid tumors. This can be accomplished by inhibiting binding of Protein C/ Activated

Protein C binding to EPCR. Any compound that interfers with this binding process will therefore be useful in the claimed method. The claims are not drawn to the compounds *per se*, only to their use. Effective compounds include non-protein molecules, antibodies to the protein, fragments of antibodies, and peptide fragments of protein C or activated protein C including the Gla domain, which is necessary for binding to EPCR.

(b) Rejections Under 35 U.S.C. § 112, First Paragraph

i. Rejection of Claims 16, 17 and 27-30 under 35 U.S.C. § 112, first paragraph

The legal standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g.*, Genentech, Inc. v. Novo Nordisk A/S, 108 F3d at 165, 42 USPQ2d at 1004 (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also In re Fisher, 427 F.2d at 839, 166 USPQ at 24; United States v. Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); In re Stephens, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (M.I.T. v. A.B. Fortia, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying

factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

> The test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.
>
> Ex parte Jackson, 217 USPQ 804, 807 (1982)

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), *citing* In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used

in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Id. at § 2164.05 (emphasis added).

In this case, the examiner has consistently relied on conclusory statements without putting forth specific reasons describing why the claims are not enabled by the specification. The patent examiner cannot just assert that the application is not enabled. As stated in In re Marzocchi at 439 F.2d 220 (CCPA 1971:

[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made [, enablement under § 112, first paragraph], to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the Appellant to go to the trouble and expense of supporting his presumptively accurate disclosure.

Id. at 224.

The Claims are enabled by the specification

The Examiner's only argument is that although the specification is enabling for antibodies and antibody fragments immunoreactive with the receptor, it does not enable making oligonucleotides and receptor fragments to bind EPCR. In this case, the examiner is relying on

conclusory statements without putting forth specific reasons describing why the claims encompassing compounds other than antibodies are not enabled by the specification. The patent examiner cannot just assert that the application is not enabled.

The different classes of compounds that could be used to block binding are described at page 18, line 20 to page 19, line 6; and methods of generating the compounds and screening them for blocking activity, are described at pages 19-34.

The specification provides evidence that compounds other than antibodies could be used to block binding of protein C or activated protein C to EPCR. See, for example, the top of page 18, which notes that incubating cells in the presence of TNF-alpha causes decreased binding of protein C or activated protein C to cells expressing EPCR. In this case the effect was indirect, by virtue of inhibition of transcription of EPCR mRNA, but also provides evidence that other inhibitors of the nucleic acid encoding EPCR would be effective in enhancing an inflammatory response by blocking binding of protein C or activated protein C to EPCR.

Additional evidence of enablement was provided with the response mailed April 27, 2001. Several papers were enclosed with this response, specifically:

Kurosawa, et al., J. Immunol. 165:4697-4703 (2000)

Gu, et al., abstract the 42nd ASH Ann. Meeting Blood 96:841a(#3516)(2000)

Joyce, eta l., J. Biochem. February 2001

Ye, et al., Biochem. Biophys. Res. Comm. 259, 671-677 (1999)

Shu, et al., FEBS Letters 477:208-212 (2000)

Tsuneyoshi, et al., Thromb. Haemost. 85:356-361 (2001)

Liaw, et al., J. Biochem. Chem. 275(8):5447-5452 (2000)

Liaw, et al., J. Biochem. 276(11):8364-8370 (2001)

Taylor, et al., Blood 95:1690-1686 (2000)

Taylor, et al., Blood 97:1685-1688 (20001)

Ye, et al., Shu, et al., and Tsuneyoshi, et al. demonstrate that antibodies to EPCR block binding to activated prtoein C and thereby inhibit protein C mediated inflammation. See also Liaw, et al., (2001) and Taylor, et al. (2000 and 2001)

Kurosawa, et al., describes studies using purified components and specific antibodies to block the reaction between EPCR and platelets and thereby the binding between EPCR and protein C or activated protein C. Blocking of binding with antibodies is shown in Figure 4 on page 4700. Blocking of binding with PR3-ANCA is shown in Figure 6.

Liaw, et al., (2000) demonstrates that soluble EPCR (a fragment of the membrane bound full length EPCR) blocks normal binding of protein C or activated protein C to membrane bound EPCR, inhibiting the activity of the protein C or activated protein C. Increased levels of soluble EPCR (up to five times normal levels) are found in patients with inflammatory disorders such as systemic lupus erythematosus and sepsis (page 5447, col. 2, bottom).

No evidence of why other compounds would not work has been provided by the examiner.

Claims 17, 27 and 28

Claims 17, 27 and 28 define the compound to be administered to enhance the inflammatory response by blocking protein C/ activated protein C to the EPCR as one of

antibodies and fragments of antibodies to the receptor, nucleic acid sequences inhibiting expression of the receptor, and synthetic or natural compounds other than proteins, peptides, or nucleic acid sequences which inhibit binding (claim 17), specifically oligonucleotides (claim 27) and receptor fragments (claim 28).

The examiner has agreed that claims to antibodies are enabled. The issue is the remaining members of the Markush group of claim 17, claim 27 and claim 28.

Methods to produce oligonucleotides are described on page 31, lines 11-31 in detail. DNA-protein interactions are known in the art and are the basis for the DNA footprinting assay. One of skill in the art would be aware of DNA-protein interactions and the ability of using nucleic acid sequences to interact with the EPCR. The gene encoding EPCR and synthesis of oligonucleotides are described in the specification. Sequences can be screened without undue experimentation using the methods described in the section beginning on page 23.

Since the gene encoding EPCR and the amino acid sequence of EPCR and binding assays to screen for fragments which bind to activated protein are described in the application, one skilled in the art would have no difficulty in practicing the claimed invention.

The examiner asserts that making non-antibody blocking compounds that bind EPCR is highly unpredictable because the function of a compound cannot be predicted by its amino acid sequence. The Examiner is wrong. Computer assisted drug design is described in the section beginning on page 26 of the specification. The principles of this approach strongly support developing novel compounds based on modeling the 3-dimensional structure of an amino acid sequence and designing new drugs to interact with that structure. The amino acid sequence is

described in the specification. Modeling systems that can be used are described on page 26, lines 26-33. There is sufficient disclosure to enable the development of non-peptide molecules that interact with the EPCR. Compounds are developed to interact with extracellular domains of the protein therefore satisfying the limitations of claim 16.

There is also a high degree of homology to the CD1 receptor family. Compounds binding to these receptors may bind to the EPCR. Screening these compounds would not require undue experimentation and the screening methods have been described in the specification on page 23. The resulting compounds are easily screened using the screening methods described in the specification. One of skill in the art would not have to undertake undue experimentation to practice the claimed method. Again, it must be emphasized that what is claimed is merely a method of enhancing an inflammatory response by blocking binding of EPCR to protein C or activated protein C. The standard for enablement is met.

Dependent claims 29 and 30 satisfy the enablement requirement

Claims 29 and 30 are drawn to the method of use of claim 16, wherein the composition includes a pharmaceutically acceptable carrier (claim 29) and is in an amount effective to enhance the inflammatory response. These claims are enabled as demonstrated by the papers discussed above.

ii. Rejection of Claims 16, 17 and 27-30 under 35 U.S.C. § 112, first paragraph

The legal standard

To satisfy the written description requirement under 35 U.S.C. 112, first paragraph, a patent specification must describe the claimed invention in sufficient detail that one skilled in the

art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g. Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116. (MPEP 2163 I.) The inquiry into adequate written description is not performed in a vacuum. "Knowledge of one skilled in the art is relevant to meeting [the written description] requirement." *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. Apr. 2, 2002) (slip op.).

Claims 16, 17, 27, and 28 satisfy the written description requirement

The Examiner's only argument is that while the specification describes methods using antibodies or antibody fragments to bind the EPCR, the specification is silent on using oligonucleotides or receptor fragments for the same purpose. The examiner is wrong.

The specification clearly encompassed the use of any compound to enhance inflammation by blocking binding of protein C/activated protein C to EPCR. See abstract on page 3; see page 18, lines 23-33. The appellants had already demonstrated that by decreasing the amount of EPCR available to bind to protein C/activated protein C through the use of a non-antibody molecule, TNF-alpha, one could enhance inflammation (top of page 18). They have demonstrated subsequently that antibodies and receptor molecules can similarly be used to enhance inflammation (see discussion above with respect to enablement) - *as originally claimed.*

The appellants provided the protein, EPCR, the sequence encoding the EPCR, methods to make antibodies thereto, means to make fragments of EPCR, and methods to assay binding. Methods for preparing receptor fragments are described on page 32. Attention is drawn to lines 8-14 which state that fragments can be used to "inhibit or compete for binding to the receptor proteins". Methods to produce oligonucleotides are described on page 31, lines 11-31 in detail.

DNA-protein interactions are known in the art and are the basis for the DNA footprinting assay. One of skill in the art would be aware of DNA-protein interactions and the ability of using nucleic acid sequences to interact with the EPCR. Synthesis of oligonucleotides is described in the specification.

Protein C/activated protein C, sequences encoding protein C/activated protein C, fragments thereof, and antibodies thereto were already known to those skilled in the art. Therefore, one skilled in the art would read the specification and know that appellants had indeed provided an adequate written description of the claimed method as of the date of filing.

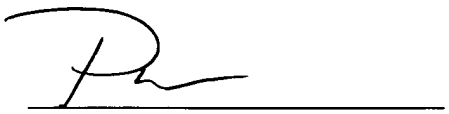
Dependent claims 29 and 30 satisfy the written description requirement

Claims 29 and 30 are directed to formulating the compound for administration (claim 29) and providing an effective amount to enhance inflammation (claim 30). Basis for these claims is found in the specification at pages 34-35 and at page 35-36 and in claims 29, and 30 as originally filed, and therefore satisfy the written description requirement.

(9) SUMMARY AND CONCLUSION

Claims 16, 17, and 27-30 comply with the requirements of 35 U.S.C. 112, first paragraph.

Respectfully submitted,



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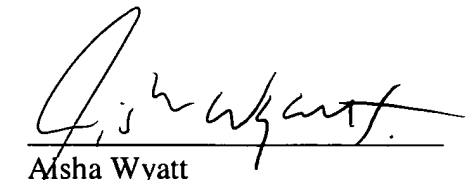

Aisha Wyatt

Date: November 22, 2002

Appendix I: Claims On Appeal

16. (amended) A method for enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor comprising administering to a patient in need of treatment thereof an amount of a compound blocking binding of protein C or activated protein C to the receptor by binding to the endothelial cell protein C/activated protein C receptor.

17. The method of claim 16 wherein the compound is selected from the group consisting of antibodies and fragments of antibodies to the receptor, nucleic acid sequences inhibiting expression of the receptor, and synthetic or natural compounds other than proteins, peptides or nucleic acid sequences which inhibit binding.

24. The method of claim 16 wherein the compound is an antibody or antibody fragment immunoreactive with the receptor.

25. The method of claim 24 wherein the antibody is humanized.

26. The method of claim 16 wherein the compound is labeled.

27. The method of claim 16 wherein the compound is an oligonucleotide.

28. The method of claim 16 wherein the compound is a receptor fragment.

29. The method of claim 16 wherein the compound is combined with a pharmaceutically acceptable carrier.

30. The method of claim 16 wherein the compound is administered in an amount effective to enhance an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor.

Appendix II: Proposed Amended Claims

16. (amended) A method for enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor comprising administering to a patient in need of treatment thereof an amount of a compound blocking binding of protein C or activated protein C to the receptor by binding to the endothelial cell protein C/activated protein C receptor.

17. The method of claim 16 wherein the compound is selected from the group consisting of antibodies and fragments of antibodies to the receptor, and synthetic or natural compounds other than proteins, or peptides which inhibit binding.

24. The method of claim 16 wherein the compound is an antibody or antibody fragment immunoreactive with the receptor.

25. The method of claim 24 wherein the antibody is humanized.

26. The method of claim 16 wherein the compound is labeled.

28. The method of claim 16 wherein the compound is a receptor fragment.

29. The method of claim 16 wherein the compound is combined with a pharmaceutically acceptable carrier.

30. The method of claim 16 wherein the compound is administered in an amount effective to enhance an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor.

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